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Efficient preparation of L-cysteic acid and its esters

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Summary. L-Cysteic acid and its esters were prepared in good yields from the oxidation of L-cystine by chlorine in water and in alcohols. When the reaction was carried out in alcohols the corresponding esters were produced.

Keywords: L-Cysteic acid – L-Cysteic acid ester – L-Cystine – Oxidation – Chlorine

Introduction

Cysteic acid, a nontoxic and nonallergenic physiologic compound, was found in human and animal blood, especially in the platelets and leukocytes. It was discovered that ichthyotic conditions may be treated with cysteic acid, homocysteic acid or cysteine sulfinic acid. Also the unpleasant odor of the body and skin disorders such as dandruff, acne, psoriasis, palmar and plantar hyperkeratosis may be treated with cysteic acid, homocysteic acid or their metal complex (Yu and Vanscott, 1977). Polycysteic acid synthesized from cysteic acid was found to inhibit the cytopathic effect of HIV-1 in CEM cell cultures at concentrations that were not cytotoxic to uninfected CEM cells (Young-im and Cushman, 1994). Applied largely in the pharmaceutical and cosmetic industry, zinc cysteate was prepared from a zinc salt, zinc oxide or hydroxide, with cysteic acid or its salts (Jean and Oliver, 1990). Hair dye agents containing cysteic acid can keep hair elastic and humid (Mustefa and Herbert, 1997). A novel non-phosphorus chelant, ethylene aspartate cysteate (EAC) sequestrants prepared from DL-cysteic acid or L-cysteic acid, can be used as a replacement for all or part of the chelants currently used in many existing laundry products (Wu et al., 1997).

Usually, L-cysteic acid was prepared from the oxidation of L-cystine in HCl solution with bromine (Clarke,

1966) or hydrogen peroxide (Lipton et al., 1977) as oxidizing reagent. The oxidation of L-cystine with dimethyl sulfoxide under the catalysis of I_2 -HCl can give L-cysteic acid (Lowe, 1977). The yields of the above strategies were acceptable but the work-ups were tedious. L-Cysteic acid esters were synthesized from esterification of L-cysteic acid with corresponding alcohols (Rosowsky et al., 1984; Tanaka and Izumiya, 1959). Herein we report an efficient preparation method of L-cysteic acid and its esters.

Results and discussion

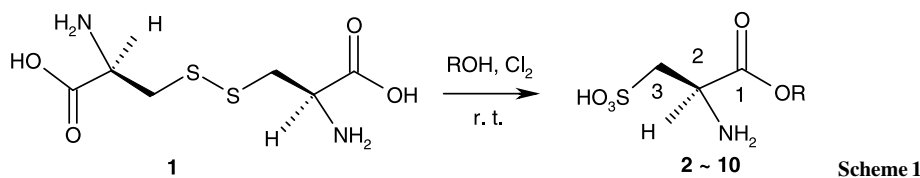
According to Scheme 1, L-cysteic acid and its esters (**2–10**) were prepared with good yields from the direct oxidation of L-cystine (**1**) by chlorine in water or alcohols at room temperature. The results are summarized in Table 1.

It should be noted that L-cystine was dissolved slowly in the corresponding solvents when chlorine was passed into the reaction vessel with stirring. The esters were precipitated from the reaction mixture, which lead to the reaction mixture solidified slowly. The solids were collected and then crystalized in methanol to give the esters. In the case of L-cysteic acid, concentration of the reaction mixture lead to the crystallization of L-cysteic acid. All of the compounds were characterized by NMR, IR and ESIMS data.

Experimental

General

Melting points were measured on an XRC-1 melting point apparatus and are uncorrected. 1H -NMR and ^{13}C -NMR spectra were recorded on a Bruker Advance 600 spectrometer with TMS as an internal standard.

**Table 1.** Oxidation of L-cystine by chlorine

Compounds	R	Solvent	Time (min)	Yield (%)
2	H	H ₂ O	15	70.3 ^a
3	CH ₃	CH ₃ OH	8	93.1 ^b
4	CH ₃ CH ₂	CH ₃ CH ₂ OH	7	84.7 ^c
5	CH ₃ CH ₂ CH ₂	CH ₃ CH ₂ CH ₂ OH	35	88.6
6	CH ₃ (CH ₂) ₂ CH ₂	CH ₃ (CH ₂) ₂ CH ₂ OH	20	85.5
7	CH ₃ (CH ₂) ₄ CH ₂	CH ₃ (CH ₂) ₄ CH ₂ OH	25	80.2
8	CH ₃ (CH ₂) ₆ CH ₂	CH ₃ (CH ₂) ₆ CH ₂ OH	35	74.6
9	(CH ₃) ₂ CH	(CH ₃) ₂ CHOH	20	82.7
10	(CH ₃) ₂ CHCH ₂	(CH ₃) ₂ CHCH ₂ OH	35	75.8

^a 81–90% (Clarke, 1966), ^b 100% from L-cysteic acid (Rosowsky et al., 1984), ^c 93% from L-cysteic acid (Tanaka and Izumiya, 1959)

ESIMS were obtained on a Finnigan LCQ^{DECA} mass spectrometer. Optical rotations were measured on a Perkin-Elmer model 341 automatic polarimeter. IR spectra were carried out on a Perkin-Elmer Spectrum One spectrometer in KBr discs.

General procedure for preparation of L-cysteic acid and its ester

1.0 g of L-cystine was suspended in 15 ml water or alcohols. Chlorine was passed into the mixture under stirring at room temperature. Excess chlorine was piped out and absorbed by 5% NaOH (aq.) solution. The reaction mixture solidified slowly. The solid was collected and crystallized from methanol to give the corresponding products.

L-Cysteic acid (2): Colorless plates crystal; m.p. 256–257°C [lit. 257–258°C (Clarke, 1966)]; $[\alpha]_D^{20} = +10.2$ (c = 3.0, 1N HCl) [lit. $[\alpha]_{54246} = +9.36$ (c = 6.0, H₂O) (Clarke, 1966)]; IR: ν_{\max} (cm⁻¹) = 3394 (NH), 3164, 3000–2500 (–COOH), 1766 (C=O), 1618, 1576, 1504, 1418, 1364, 1240, 1220, 1169, 1032 and 711 (S=O), 1131, 1082, 1062, 966, 876, 847, 795, 643, 578, 538 and 514; ¹H-NMR (600 MHz, D₂O): δ = 4.36 (1H, dd, *J* = 8.4, 3.3 Hz, 2-H), 3.46 (1H, dd, *J* = 15.1, 3.3 Hz, 3-Ha), 3.34 (1H, dd, *J* = 15.1, 8.4 Hz, 3-Hb); ESIMS (negative mode) *m/z* (rel. int.): 168 ([M – H][–], 100).

Methyl L-cysteate (3): White solid; m.p. 220–224°C; $[\alpha]_D^{20} = +8.5$ (c = 3.0, 1N HCl); IR: ν_{\max} (cm⁻¹) = 3478 (NH), 3177, 3023, 2984, 2920, 1749 (C=O), 1595, 1496, 1442, 1424, 1373, 1334, 1290, 1273, 1226, 1179, 1032 and 741 (S=O), 1140, 1102, 978, 931, 889, 846, 803, 623, 600 and 533; ¹H-NMR (600 MHz, D₂O): δ = 4.58 (1H, dd, *J* = 7.1, 3.8 Hz, 2-H), 3.85 (3H, s, –OCH₃), 3.55 (1H, dd, *J* = 15.1, 3.8 Hz, 3-Ha), 3.49 (1H, dd, *J* = 15.1, 7.1 Hz, 3-Hb); ¹³C-NMR (150 MHz, D₂O): δ = 168.8, 54.3, 50.0, 49.2; ESIMS (negative mode) *m/z* (rel. int.): 182 ([M – H][–], 100).

Ethyl L-cysteate (4): White solid; m.p. 244–246°C [lit. 238–240°C (Tanaka et al., 1959)]; $[\alpha]_D^{20} = -8.9$ (c = 3.0, 1N HCl) [lit. $[\alpha]_D^{20} = +4.1$ (c = 2.0, H₂O) (Tanaka et al., 1959)]; IR: ν_{\max} (cm⁻¹) = 3465 (NH), 2985, 1748 (C=O), 1603, 1507, 1419, 1382, 1339, 1190, 1042 and 738 (S=O), 1092, 968, 859, 798, 592 and 524; ¹H-NMR (600 MHz, D₂O): δ = 4.53

(1H, dd, *J* = 7.2, 3.8 Hz, 2-H), 4.30 (2H, q, *J* = 7.0 Hz, –OCH₂CH₃), 3.54 (1H, dd, *J* = 15.1, 3.8 Hz, 3-Ha), 3.48 (1H, dd, *J* = 15.1, 7.2 Hz, 3-Hb), 1.29 (3H, t, *J* = 7.0 Hz, –OCH₂CH₃); ¹³C-NMR (150 MHz, D₂O): δ = 168.2, 64.3, 50.0, 49.2, 13.3; ESIMS (negative mode) *m/z* (rel. int.): 196 ([M – H][–], 100).

n-Propyl L-cysteate (5): White solid; m.p. 248–250°C; $[\alpha]_D^{20} = -1.6$ (c = 3.0, 1N HCl); IR: ν_{\max} (cm⁻¹) = 3470 (NH), 3086, 2970, 2940, 1744 (C=O), 1618, 1504, 1466, 1395, 1376, 1291, 1272, 1250, 1220, 1185, 1047 and 733 (S=O), 1107, 1070, 927, 873, 855, 812, 588, 547 and 524; ¹H-NMR (600 MHz, D₂O): δ = 4.49 (1H, dd, *J* = 7.2, 3.8 Hz, 2-H), 4.14 (2H, m, –OCH₂CH₂CH₃), 3.48 (1H, dd, *J* = 15.1, 3.8 Hz, 3-Ha), 3.43 (1H, dd, *J* = 15.1, 7.2 Hz, 3-Hb), 1.62 (2H, m, –OCH₂CH₂CH₃), 0.85 (3H, t, *J* = 7.4 Hz, –OCH₂CH₂CH₃); ¹³C-NMR (150 MHz, D₂O): δ = 168.4, 69.7, 50.0, 49.2, 21.4, 9.7; ESIMS (negative mode) *m/z* (rel. int.): 210 ([M – H][–], 100).

n-Butyl L-cysteate (6): White solid; m.p. 197–198°C; $[\alpha]_D^{20} = -3.0$ (c = 3.0, 1N HCl); IR: ν_{\max} (cm⁻¹) = 3436 (NH), 3185, 2959, 2681, 1750 (C=O), 1592, 1534, 1468, 1420, 1402, 1378, 1276, 1251, 1193, 1039 and 743 (S=O), 1078, 931, 823, 589, 540 and 523; ¹H-NMR (600 MHz, D₂O): δ = 4.54 (1H, dd, *J* = 7.3, 3.8 Hz, 2-H), 4.27 (2H, m, –OCH₂CH₂CH₂CH₃), 3.54 (1H, dd, *J* = 15.1, 3.8 Hz, 3-Ha), 3.48 (1H, dd, *J* = 15.1, 7.3 Hz, 3-Hb), 1.66 (2H, m, –OCH₂CH₂CH₂CH₃), 1.37 (2H, m, –OCH₂CH₂CH₂CH₃), 0.89 (3H, t, *J* = 7.4 Hz, –OCH₂CH₂CH₂CH₃); ¹³C-NMR (150 MHz, D₂O): δ = 168.3, 68.0, 49.9, 49.2, 29.8, 18.6, 13.1; ESIMS (negative mode) *m/z* (rel. int.): 224 ([M – H][–], 100). ESIMS (positive mode) *m/z* (rel. int.): 226 ([M + H]⁺, 100).

n-Hexyl L-cysteate (7): White needles; m.p. 194–196°C; $[\alpha]_D^{20} = +9.3$ (c = 0.3, MeOH); IR: ν_{\max} (cm⁻¹) = 3470 (NH), 2595, 2860, 1745 (C=O), 1602, 1535, 1469, 1421, 1397, 1376, 1341, 1223, 1150, 1039 and 737 (S=O), 1090, 1070, 999, 908, 886, 797, 643, 606, 534 and 521; ¹H-NMR (600 MHz, D₂O): δ = 4.48 (1H, dd, *J* = 7.3, 3.8 Hz, 2-H), 4.20 (2H, m, –OCH₂CH₂CH₂(CH₂)₂CH₃), 3.48 (1H, dd, *J* = 15.1, 3.8 Hz, 3-Ha), 3.42 (1H, dd, *J* = 15.1, 7.3 Hz, 3-Hb), 1.62 (2H, m, –OCH₂CH₂CH₂(CH₂)₂CH₃), 1.30 (2H, m, –OCH₂CH₂CH₂(CH₂)₂CH₃), 1.23 (4H, m, –OCH₂CH₂CH₂(CH₂)₂CH₃), 0.79 (3H, t, *J* = 7.1 Hz, –OCH₂CH₂CH₂(CH₂)₂CH₃);

^{13}C -NMR (150 MHz, D_2O): δ = 168.4, 68.3, 50.0, 49.2, 30.8, 27.7, 24.9, 22.1, 13.5; ESIMS (negative mode) m/z (rel. int.): 252 ($[\text{M} - \text{H}]^-$, 100).

n-Octyl L-cysteate (**8**): White needles; m.p. 184–188°C; $[\alpha]_D^{20}$ = +7.0 (c = 0.3, MeOH); IR: ν_{max} (cm^{-1}) = 3473 (NH), 2926, 2856, 1746 (C=O), 1601, 1536, 1468, 1420, 1399, 1377, 1340, 1195, 1040 and 736 (S=O), 1090, 945, 883, 847, 821, 736, 606, 591 and 532; ^1H -NMR (600 MHz, CD_3OD): δ = 4.40 (1H, dd, J = 9.2, 3.1 Hz, 2-H), 4.26 (2H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 3.37 (1H, dd, J = 14.6, 3.1 Hz, 3-Ha), 3.24 (1H, dd, J = 14.6, 9.2 Hz, 3-Hb), 1.72 (2H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 1.39 (2H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 1.32 (8H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 0.90 (3H, t, J = 7.0 Hz, $-\text{OCH}_2\text{CH}_2\text{CH}_2(\text{CH}_2)_4\text{CH}_3$); ^{13}C -NMR (150 MHz, CD_3OD): δ = 167.7, 67.0, 50.2, 49.1, 31.7, 29.1, 28.2, 25.6, 22.5, 13.2; ESIMS (negative mode) m/z (rel. int.): 280 ($[\text{M} - \text{H}]^-$, 100).

iso-Propyl L-cysteate (**9**): White solid; m.p. 220–224°C; $[\alpha]_D^{20}$ = –16.5 (c = 1.0, 1N HCl); IR: ν_{max} (cm^{-1}) = 3461 (NH), 3196, 2977, 2676, 1744 (C=O), 1590, 1533, 1470, 1422, 1383, 1341, 1276, 1195, 1039 and 742 (S=O), 1101, 1076, 975, 929, 897, 853, 827, 656, 589, 541 and 524; ^1H -NMR (600 MHz, D_2O): δ = 5.1 (1H, m, $-\text{OCH}(\text{CH}_3)_2$), 4.49 (1H, dd, J = 7.5, 3.8 Hz, 2-H), 3.52 (1H, dd, J = 15.1, 3.8 Hz, 3-Ha), 3.47 (1H, dd, J = 15.1, 7.5 Hz, 3-Hb), 1.28 (6H, m, $-\text{OCH}(\text{CH}_3)_2$); ^{13}C -NMR (150 MHz, D_2O): δ = 167.6, 73.2, 50.0, 49.1, 20.9, 20.8; ESIMS (negative mode) m/z (rel. int.): 210 ($[\text{M} - \text{H}]^-$, 100).

iso-Butyl L-cysteate (**10**): Colorless plates crystal; m.p. 268–270°C; $[\alpha]_D^{20}$ = –2.2 (c = 1.5, 1N HCl); IR: ν_{max} (cm^{-1}) = 3468 (NH), 3116, 2991, 2958, 2878, 2737, 2678, 1748 (C=O), 1582, 1505, 1471, 1423, 1402, 1388, 1373, 1289, 1196, 1043 and 733 (S=O), 1075, 994, 962, 944, 921, 871, 856, 833, 808, 673, 590, 546 and 523; ^1H -NMR (600 MHz, D_2O): δ = 4.51 (1H, dd, J = 7.1, 4.0 Hz, 2-H), 3.98 (2H, m, $-\text{OCH}_2\text{CH}(\text{CH}_3)_2$), 3.48 (1H, dd, J = 15.1, 4.0 Hz, 3-Ha), 3.44 (1H, dd, J = 15.1, 7.1 Hz, 3-Hb), 1.92 (1H, m, $-\text{OCH}_2\text{CH}(\text{CH}_3)_2$), 0.86 (6H, d, J = 6.8 Hz, $-\text{OCH}_2\text{CH}(\text{CH}_3)_2$); ^{13}C -NMR (150 MHz, D_2O): δ = 168.4, 73.9, 50.0, 49.2, 18.3; ESIMS (negative mode) m/z (rel. int.): 224 ($[\text{M} - \text{H}]^-$, 100).

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